

### **REMARKS**

Claims 19, 23-34 and 37 are currently pending in the present application. Claim 19 is the only independent claim. Claims 20-22 have been cancelled without prejudice or disclaimer. Claims 19 and 23-31 are under examination on the merits. The Examiner has withdrawn claims 32-34 from consideration as being directed to a non-elected invention. Since new claim 37, directed to the milk of claim 33, supported at least by the first paragraph at page 25, and original claim 16 as filed, depends from non-elected and withdrawn claim 33, claim 37 is listed as being withdrawn, even though it has yet to be examined.

For clarity, without prejudice or disclaimer, claims 19, 23-25, 27, 28 and 32-34, have been amended, and Claim 37 is newly added. As discussed below under "Claim Rejections-35 USC §112," and "Claim Rejections for Obviousness," Applicants respectfully submit that the amendments made herein are supported by the specification and the original claims and introduce no new subject matter. Entry of the amendments made herein is proper and respectfully requested.

### **Restriction Requirement**

The Examiner indicated at page 2 of the detailed action that claims 32-34 do not clearly set forth that the milk collected from the non-human transgenic mammal of claim 19, from which claims 32 and 34 directly or indirectly depend, or of claim 22, from which claim 33 and new claim 37 directly or indirectly depend, do not clearly set forth having the FVIII protein. Applicants respectfully point out that claims 32-34 and 37 each specifically recite the FVIII protein. The Examiner apparently has overlooked this or Applicants misunderstand the Examiner's statement. Further explanation and reconsideration and withdrawal of the restriction requirement are respectfully requested, since if the mammal from which the milk is collected is patentable, for the reasons discussed below, then the milk collected from the mammal should be patentable.

### **Claim Rejections 35 USC §112**

Claim 27 is rejected under 35 USC §112, first and paragraph, as failing to comply with the written description requirement and as being indefinite in view of the prior recitation of "up

to about 50 mg of the B-domain deleted human FVIII polypeptide per liter of the milk.” Claim 27 has been amended to overcome the objection by deleting “about”, which is supported at least first paragraph at page 25 (50.2 µg per ml is 50.2 mg per liter), and original claim 16 as filed. The same amendment has been made in withdrawn claim 34. Withdrawal of the rejection of claim 27 for lack of an adequate written description is respectfully requested. Claims 34 and new claim 37, which contain the same language, should also be considered supported and definite.

### **Claim Rejections for Obviousness**

The Examiner has rejected claims 19-21 and 24-31 under 35 USC §103(a) as being unpatentable over Chen, *Transgenic Research*, 11:257-268, 2002 (“Chen”) in view of Soukharev, *Blood Cells, Molecules and Diseases*, 28:234-248, 2002 (“Soukharev”) and supported by Lubon U.S. Patent 6,255,554 (“Lubon”).

Reconsideration and withdrawal of the rejection and allowance of the pending claims are respectfully requested, particularly in view of the amendment to claim 19 by incorporating two unexpected features that were neither taught nor suggested by the cited references, alone or in combination, as well as Dr. Chen’s Declaration as filed on December 26, 2007 (“Dr. Chen’s Declaration”), for the following reasons.

As stated on page 5 of Dr. Chen’s Declaration and as recognized in the outstanding Office Action at page 8, lines 7-13 and page 12, line 18, to page 13, line 3, the references do not teach or suggest transgenic non-human mammals that secrete the B-domain deleted human FVIII polypeptide with an increased activity in milk that Applicants were the first to have actually successfully generated when the mammals are lactating, where the increase in activity is caused by the previously unclaimed bovine  $\alpha$ -S1 casein signal peptide sequence and a new recombinant spliced site (Ser 741 link to Leu 1643). The prior art does not provide an enabling disclosure with a reasonable expectation of success concerning these features. These aspects are now specifically recited in claim 19, the only pending independent claim directed to the non-human transgenic mammal, as well as in claim 28, directed to the method of making the non-human transgenic mammal. Thus, the claimed invention, distinct from the prior art, even as combined, correlates to the data in the application and to the evidence of unexpected results and beneficial

properties presented in Dr. Chen's Declaration. Accordingly, the rejection of claim 19 and its dependent claims for obviousness has been overcome by incorporating the two unexpected features.

More particularly, according to Dr. Chen's Declaration, the presently claimed transgenic mammals provide superior and unexpected results over the prior art, and would not have been obvious over the prior art, for at least the following reasons:

(a) the presently claimed transgenic mammals secreted B-domain deleted FVIII protein into the milk at a high yield. The average concentration of the secreted B-domain deleted FVIII protein in milk was up to 50 µg/ml, which is about 250-fold more concentrated than that of the normal human plasma (please refer to Supplement Table 1 in Dr. Chen's Declaration, showing that the concentration of the secreted B-domain deleted FVIII protein was higher than that of the secreted full-length FVIII protein as reported in the prior art); and

(b) the B-domain deleted FVIII protein secreted in the milk of the transgenic mammals had an increased clotting activity. Chen discloses that "only 5-10% of biological activity of recombinant hFVIII protein produced by transgenic mammary gland was detected by clotting assay as compared with ELISA protein quantification" (page 265).

Page 241 of Soukharev also recognizes the lower activity of transgenic hFVIII protein in milk due to FVIII interaction with milk proteins. As shown in Supplement Table 2 in Dr. Chen's Declaration, based on the clotting activity of BDD-rFVIII protein detected in milk of the transgenic mammary glands, about 10-15% biological activity was detected for the BDD-rFVIII protein secreted in milk compared with ELISA protein quantification. This is unexpected, because none of the prior art references has suggested or in any other way recognized that the use of BDD-rFVIII would not only increase the yield, but also improve the clotting activity, of rFVIII in the milk.

The cited prior art references do not render the present claims obvious, because the BDD-rFVIII construct used in transgenic mammals of the present application is different from those used in the cell line expression systems in the prior art. As stated in Dr. Chen's Declaration, there was no need to modify the signal sequence for the BDD-rFVIII protein in constructs for the cell line expression systems. The native 19 amino acid secretion signal peptide of the human FVIII is sufficient to direct the secretion of the BDD-rFVIII protein in the cell line expression

systems. However, in constructs used for transgenic mammals, the native 19 amino acid secretion signal peptide of the human FVIII must be replaced by a bovine  $\alpha$ -S1 casein signal peptide to allow efficient secretion of the BDD-rFVIII protein into mammary glands. In addition, as shown in Supplement Table 3 in Dr. Chen's Declaration, a new recombinant splice site or fusion junction, Ser 741 link to Lys 643 of the amino acid sequence of the full length human FVIII, was used for more complete B-domain deletion sequence in the construct of the present invention. This new recombinant splice site is not described or suggested anywhere in the cited prior art references.

Applicants therefore respectfully request that the rejections under 35 USC §103(a) over the prior art references be reconsidered and withdrawn.

Applicants respectfully submit that claims 19 and 23-31 are in condition for allowance and such action is respectfully requested.

Because claims 32-34 and 37 depend from and include all elements of claim 19, Applicants respectfully request the rejoinder of claims 32-34 and the inclusion of claim 37 for substantive examination and corresponding allowance based upon the allowability of claim 19. The allowance of claims 32-34 and 37 is also respectfully requested based on the finding of allowability of claim 19.

Respectfully submitted,

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